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Soluble Fas in the Serum of Patients With Non-Hodgkin's Lymphoma: Higher Concentrations in Angioimmunoblastic T-Cell Lymphoma

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The soluble form of Fas (sFas) can block apoptosis induced by the Fas ligand in vitro. A recent report demonstrated that mice injected with sFas displayed autoimmune features. Therefore, an elevated serum concentration of sFas may be associated with lymphoproliferation and autoimmune diseases. We measured the serum concentrations of sFas in 77 patients with non-Hodgkin's lymphoma (NHL) [8 angioimmunoblastic T-cell lymphoma (AIL), 12 T-cell NHL, 53 B-cell NHL, and 4 natural killer-cell NHL]. Elevated concentrations of sFas were detected only in AIL, which is frequently accompanied by autoimmune diseases ($P < 0.005$ compared with age-matched controls). A possible association of sFas and autoimmune features in AIL is discussed. Am. J. Hematol. 58:334–336, 1998.

Key words: soluble Fas; apoptosis; non-Hodgkin's lymphoma; angioimmunoblastic T-cell lymphoma

INTRODUCTION

Mutations in the Fas gene and the Fas ligand gene have been shown to be the primary defects in the murine and human inherited autoimmune lymphoproliferative syndrome (ALPS) [1–4]. Defects in the Fas pathway are associated with the abnormal proliferation of lymphoid cells, and autoimmune diseases.

Soluble isoforms of the Fas molecule (sFas) have been identified [5]. Cheng et al. [5] have reported higher serum concentrations of sFas in patients with systemic lupus erythematosus. They have also reported that mice injected with sFas display autoimmune features. Papoff et al. [6] have shown that sFas blocks apoptosis induced by the Fas ligand in vitro. Although the physiologic functions of sFas remain to be clarified, an elevated serum concentration of sFas may be associated with a condition similar to that induced by abnormalities of Fas or the Fas ligand molecule by inhibiting apoptosis in susceptible cells.

Angioimmunoblastic T-cell lymphoma (AIL) is a peripheral T-cell lymphoma characterized by systemic lymphadenopathy, hepatosplenomegaly, a skin rash, polyclonal hypergamma-globulinemia, and frequent autoimmune features [7,8]. These findings resemble the abnormalities caused by mutations of the Fas gene. In addition, the histology of an enlarged lymph node from a patient with ALPS has been reported to show atypical T-cell hyperplasia resembling AIL [2]. We, therefore, measured the serum concentrations of sFas in patients with AIL and other non-Hodgkin's lymphomas (NHL), and compared them with serum sFas concentrations in healthy subjects.

PATIENTS AND METHODS

Patients' Sera

Serum was obtained from 77 untreated patients with NHL [8 AIL, 12 T-cell NHL (T-NHL), 53 B-cell NHL (B-NHL), and 4 natural killer-cell NHL (NK)]. T-NHL consists of various types of peripheral T-cell lymphoma

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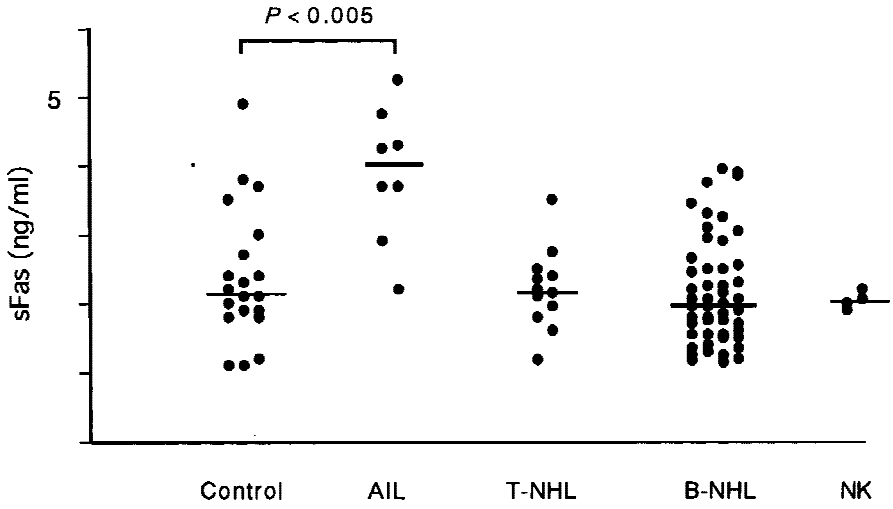

Fig. 1. Serum concentration of sFas in patients with non-Hodgkin's lymphoma (NHL). Horizontal bars indicate the median sFas concentration for the respective group. AIL, angioimmunoblastic T-cell lymphoma; T-NHL, T-cell NHL; B-NHL, B-cell NHL; NK, natural killer-cell NHL.

other than AIL. All were negative for HTLV-I antibody. The B-NHL group included only diffuse lymphomas (30 large cell, 4 large cell/immunoblastic, 5 small cleaved cell, 6 mixed, 4 mucosa-associated lymphoid tissue lymphomas, and 4 other lymphomas). Sera from 20 healthy subjects were used for the control group. The sera were stored at −20°C until use.

Measurement of sFas

sFas in the stored sera was measured with a sandwich enzyme-linked immunosorbent assay (ELISA) kit (sFas ELISA kit, Medical & Biological Laboratories Co., Nagoya, Japan), according to the manufacturer's instructions. The data are shown as the mean values of duplicate samples.

Statistical Analyses

Comparisons of age and the sFas concentrations between groups were calculated using the nonparametric Mann-Whitney U-test.

RESULTS

A recent report has demonstrated a positive correlation between serum sFas concentrations and age in healthy subjects [9]. The median age of the control group was 61 years. The median ages of the AIL, T-NHL, B-NHL, and NK groups were 61, 62, 62, and 55 years, respectively. No significant differences were found in the median age between the control group and the various NHL groups.

The median serum sFas concentration was significantly higher in the AIL group (median 3.98 ng/ml, range 2.20–5.25 ng/ml) than in the control group (median 2.15 ng/ml, range 1.10–4.90 ng/ml) ($P < 0.005$) (Fig. 1). No significant difference was found among the median sFas concentrations of the control group and those of the T-NHL, B-NHL, and NK groups. All patients with AIL had advanced-stage disease [clinical stage (CS) III or IV], which may have been the cause of the elevation of the sFas concentration in the AIL group. Therefore, we compared the sFas concentrations in CS III or IV B-NHL ($n = 26$) with those of the control group. However, no significant difference was found between them.

DISCUSSION

Among the various types of NHL patients examined in this study, only patients with AIL had a significantly higher serum concentration of sFas, as compared with the age-matched controls. A significantly higher serum concentration of sFas has been reported in patients with B-NHL [10]. Although the reason for the difference between their results and ours is not clear, differences in the histologic subtypes included in the B-NHL group and in the anti-Fas antibodies used for the ELISA may explain them.

The role of the higher serum concentration of sFas in AIL remains to be determined. It seems unlikely that abnormalities of the Fas/Fas ligand system would be involved in the pathogenesis of AIL per se, as most of the patients with ALPS do not develop lymphoma [2–4]. However, the increased sFas concentration may affect the clinical features of AIL. One of the most prominent features of AIL is a high frequency of autoimmune diseases. As mentioned above, it has been suggested that an elevated serum concentration of sFas may be associated with autoimmune-like conditions [5]. Therefore, it appears possible that the elevated serum concentration of sFas may have some association with the development of autoimmune features in AIL. However, it is clear that the elevation of serum sFas does not directly cause autoimmune diseases, because some healthy elderly subjects had high serum concentrations of sFas, comparable to those seen in the patients with AIL. The association between sFas and autoimmune diseases in AIL, if any, appears to be complicated by other factors.

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